AMENDMENTS TO THE SPECIFICATION

Please replace the paragraph beginning on line 6, page 1, with the following amended paragraph:

This invention is a method for the treatment of *Flaviviridae* infection in a host, such as a human, in need of such therapy, that includes the administration of a 2'-branched nucleoside, or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation. The invention also includes a method for the treatment of *Flaviviridae* infection in a host, such as a human, in need of such therapy, that includes the administration of a 2'-branched nucleoside, or a pharmaceutically acceptable salt, ester, or prodrug thereof, in combination and/or alternation with interferon. The invention also includes a method to detect a mutant strain of *Flaviviridae* and a method for its treatment, and kits and materials for such detection.

Please replace the paragraph beginning on line 4, page 11, with the following amended paragraph:

It has been discovered that prolonged use of a 2'-branched nucleoside, for example a 2'-branched nucleoside depicted below, and in particular, a 2'-branched pyrimidine nucleoside, such as the compound β-D-2'-CH_3-riboC, or a 2'-branched purine nucleoside, including the compound β-D-2'-CH_3-riboAdenosine or β-D-2'-CH3-ribo-6-N-methyl amino adenosine, is associated with a mutation at a nucleotide that encodes for serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region (**Figure 11**) of *Flaviviridae*, which results in a change in the amino acid residue serine to a different amino acid, for example, threonine. This domain is found in

the NS5B region of the HCV genome, as well as in genomes of other flaviviruses. It is highly conserved among all hepaci-, pesti- and flavivirus genomes (**Figure 11**, Lai et al. J Virol. **1999**, *73*, 10129-36).

Please replace the paragraphs beginning on line 16, page 14, with the following amended paragraphs:

In the case of BVDV infection, 2'-branched nucleosides, and, in particular, 2'-branched pyrimidine nucleosides such as the compound β-D-2'-CH_3-riboC induce a mutation from a guanine (G) to cytidine (C) at reside 1214 of the RNA polymerase of BVDV, which results in a change in the amino acid residue serine to threonine at position 405 of ~~of~~ the enzyme. This serine residue is located in the conserved consensus sequence (XRXSGXXXT (Sequence ID No. 63)) of the RNA polymerase domain B (**Figures 5** and **11**), identified by mutational analysis (Lai V. C., Kao C.C., Ferrari E., Park J., Uss A.S., Wright-Minogue J., Hong Z., and J.Y. Lau. "Mutational analysis of bovine viral diarrhea virus RNA-dependent RNA polymerase" J Virol. **1999**, *73*, 10129-36).

In the case of HCV infection, 2'-branched nucleosides, and, in particular, 2'-branched pyrimidine nucleosides such as the compound β-D-2'-CH_3-riboC induce a mutation at a nucleotide that encodes for $Serine_{282}$ in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region (**Figure 11**), which results in a change from serine to a different amino acid, such as threonine.

Please replace the paragraph beginning on line 11, page 15, with the following amended paragraph:

One aspect of the present invention provides a method to treat a *Flaviviridae* infection by administering a therapeutically effective amount of a 2'-branched nucleoside, for example, a 2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC, or its pharmaceutically acceptable prodrug and/or salt, to a host, such as a human, in need of such therapy, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a

change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation. This highly conserved serine residue corresponds to amino acid position 405 of the RNA polymerase region of the BVDV genome. It also corresponds to amino acid position 282 of the RNA polymerase region of the HCV genome (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36).

Please replace the paragraph beginning on line 3, page 16, with the following amended paragraph:

(i) A pharmaceutical composition effective for the treatment of a *Flaviviridae* infection in a host, such as a human, comprising an effective amount of a 2'-branched nucleoside, for example, a 2'-branched nucleoside, such as β-D-2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC or a prodrug, such as the 3'-valine ester prodrug of β-D-2'-CH_3-riboC, or a β-D-2'-branched purine nucleoside, for example β-D-2'-CH_3-riboA or β-D-2'-CH_3-ribo-6-N-methylaminopurine or a prodrug, such as the 3'-valine ester prodrug, or its pharmaceutically acceptable prodrug and/or salt, optionally in a pharmaceutically acceptable carrier or diluent, in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example, other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36), and/or one or more drugs that are associated with such a mutation.

Please replace the paragraphs beginning on line 12, page 17, with the following amended paragraphs:

in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

(iv) A method for treating a *Flaviviridae* infection in a host, such as a human, comprising administering an effective amount of a 2'-branched nucleoside, such as β-D-2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC or a prodrug, such as the 3'-valine ester prodrug of β-D-2'-CH_3-riboC, or a β-D-2'-branched purine nucleoside, for example β-D-2'-CH_3-riboA or β-D-2'-CH_3-ribo-6-N-methylaminopurine or a prodrug, such as the 3'-valine ester prodrug, or its pharmaceutically acceptable prodrug and/or salt to the human, optionally in a pharmaceutically acceptable carrier or diluent, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example, other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36), and/or one or more drugs that are associated with such a mutation.

Please replace the paragraph beginning on line 5, page 19, with the following amended paragraph:

in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved

consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

Please replace the paragraph beginning on line 29, page 19, with the following amended paragraph:

(a) contacting a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complementary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of *Flaviviridae* (**Figure 11**);

Please replace the paragraph beginning on line 16, page 22, with the following amended paragraph:

(b) contacting the sample with a detectable oligonucleotide probe having a sequence complementary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of *Flaviviridae* (**Figure 11**);

Please replace the paragraphs beginning on line 21, page 24, with the following amended paragraphs:

The protein, peptide or peptide fragment can be confirmed by reaction with an antibody, preferably a monoclonal antibody, for example using a Western blot method. Alternatively, the protein or peptide can be isolated and sequenced or otherwise identified by any means known in the art, including by 2D PAGE. In one embodiment, a reactive antibody binds to an *Flaviviridae* protein or peptide sequence that includes a threonine rather than serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example at position 405 of the RNA

polymerase region of BVDV genome or at position 282 of the RNA polymerase region of the HCV genome.

In another embodiment, the reactive antibody binds specifically to a peptide sequence that includes a threonine rather than serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example at position 405 of the RNA polymerase region of BVDV genome or at position 282 of the RNA polymerase region of the HCV genome, which represent a specific point mutations in the RNA polymerase region of *Flaviviridae* that is correlated with therapy failure.

Please replace the paragraphs beginning on line 23, page 26, with the following amended paragraphs:

It has been discovered that prolonged use of a 2'-branched nucleoside, for example a 2'-branched nucleoside depicted below, and in particular, a 2'-branched pyrimidine nucleoside such as the compound β-D-2'-CH_3-riboC, is associated with a mutation at a nucleotide that encodes for serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region (**Figure 11**) of *Flaviviridae* resulting in a change in the amino acid residue serine to a different amino acid, for example, threonine. This domain is found in the NS5B region of the HCV genome, as well as in genomes of other flaviviruses. It is highly conserved among all hepaci-, pesti- and flavivirus genomes (**Figure 11**, Lai et al. J Virol. **1999**, *73*, 10129-36).

In the case of BVDV infection, 2'-branched nucleosides, and, in particular, 2'-branched pyrimidine nucleosides such as the compound β-D-2'-CH_3-riboC induce a mutation from a guanine (G) to cytidine (C) at reside 1214 of the RNA polymerase of BVDV causing a change in the amino acid residue serine to threonine at position 405 of ~~of~~ the enzyme. This serine residue is located in the conserved consensus sequence (XRXSGXXXT (Sequence ID No. 63)) of the RNA polymerase domain B (**Figures 5** and **11**), identified by mutational analysis (Lai V. C., Kao C.C., Ferrari E., Park J., Uss A.S., Wright-Minogue J., Hong Z., and J.Y. Lau. "Mutational analysis of bovine viral diarrhea virus RNA-dependent RNA polymerase" J Virol. **1999**, *73*, 10129-36).

In the case of HCV infection, 2'-branched nucleosides, and, in particular, 2'-branched pyrimidine nucleosides such as the compound β-D-2'-CH_3-riboC induce a mutation at a nucleotide that encodes for $Serine_{282}$ in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region (**Figure 11**) resulting in a change from serine to a different amino acid, such as threonine.

Please replace the paragraph beginning on line 28, page 27, with the following amended paragraph:

One aspect of the present invention provides a method to treat a *Flaviviridae* infection by administering a therapeutically effective amount of a 2'-branched nucleoside, for example, a 2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC, or its pharmaceutically acceptable prodrug and/or salt, to a host, such as a human, in need of such therapy, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation. This highly conserved serine residue corresponds to amino acid position 405 of the RNA polymerase region of the BVDV genome. It also corresponds to amino acid position 282 of the RNA polymerase region of the HCV genome (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36).

Please replace the paragraph beginning on line 20, page 28, with the following amended paragraph:

(i) A pharmaceutical composition effective for the treatment of a *Flaviviridae* infection in a host, such as a human, comprising an effective amount of a 2'-branched nucleoside, for example, a 2'-branched nucleoside, such as β-D-2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC or a prodrug, such as the 3'-valine ester prodrug of β-D-2'-CH_3-riboC, or a β-D-2'-branched purine nucleoside, for example β-D-2'-CH_3-riboA or β-D-2'-CH_3-ribo-6-N-methylaminopurine or a prodrug, such as the

3'-valine ester prodrug, or its pharmaceutically acceptable prodrug and/or salt, optionally in a pharmaceutically acceptable carrier or diluent, in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example, other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36), and/or one or more drugs that are associated with such a mutation.

Please replace the paragraphs beginning on line 30, page 29, with the following amended paragraphs:

in combination with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

(iv) A method for treating a *Flaviviridae* infection in a host, such as a human, comprising administering an effective amount of a 2'-branched nucleoside, such as β-D-2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC or a prodrug, such as the 3'-valine ester prodrug of β-D-2'-CH_3-riboC, or a β-D-2'-branched purine nucleoside, for example β-D-2'-CH_3-riboA or β-D-2'-CH_3-ribo-6-N-methylaminopurine or a prodrug, such as the 3'-valine ester prodrug, or its pharmaceutically acceptable prodrug and/or salt to the human, optionally in a pharmaceutically acceptable carrier or diluent, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example, other than nucleotide 1214 (G to C) or 405 Ser to Thr of the RNA polymerase region

of BVDV or nucleotide 8443 (G to C) of the HCV genome or 282 Ser to Thr of the RNA polymerase region of HCV (**Figure 11**; Lai et al. J Virol., **1999**, *73*, 10129-36), and/or one or more drugs that are associated with such a mutation.

Please replace the paragraph beginning on line 22, page 31, with the following amended paragraph:

in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

Please replace the paragraph beginning on line 16, page 32, with the following amended paragraph:

(a) contacting a sample containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complementary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of *Flaviviridae* (**Figure 11**);

Please replace the paragraph beginning on line 9, page 35, with the following amended paragraph:

(b) contacting the sample with a detectable oligonucleotide probe having a sequence complementary a codon that encodes a serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of *Flaviviridae* (**Figure 11**);

Please replace the paragraphs beginning on line 14, page 37, with the following amended paragraphs:

The protein, peptide or peptide fragment can be confirmed by reaction with an antibody, preferably a monoclonal antibody, for example using a Western blot method. Alternatively, the protein or peptide can be isolated and sequenced or otherwise identified by any means known in the art, including by 2D PAGE. In one embodiment, a reactive antibody binds to an *Flaviviridae* protein or peptide sequence that includes a threonine rather than serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example at position 405 of the RNA polymerase region of BVDV genome or at position 282 of the RNA polymerase region of the HCV genome.

In another embodiment, the reactive antibody binds specifically to a peptide sequence that includes a threonine rather than serine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, for example at position 405 of the RNA polymerase region of BVDV genome or at position 282 of the RNA polymerase region of the HCV genome, which represent a specific point mutations in the RNA polymerase region of *Flaviviridae* that is correlated with therapy failure.

Please replace the paragraph beginning on line 9, page 79, with the following amended paragraph:

(iii) administering an effective amount of one or more drugs that in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that are associated with such a mutation.

Please replace the paragraph beginning on line 23, page 79, with the following amended paragraph:

(iii) administering an effective amount of one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine at position 282 to a different amino acid, such as threonine, in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that is associated with such a mutation.

Please replace the paragraph beginning on line 7, page 80, with the following amended paragraph:

(iii) administering an effective amount of one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine at position 405 to a different amino acid, such as threonine, in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that is associated with such a mutation.

Please replace the paragraphs beginning on line 1, page 84, with the following amended paragraphs:

In a further embodiment, the invention provides a method for assaying a sample suspected of containing a Thr instead of a Ser in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of a *Flaviviridae,* which indicates that the virus is hypersensitive to interferon treatment, comprising:

(i) contacting a sample suspected of containing a *Flaviviridae* nucleic acid sequence with a detectable oligonucleotide probe having a sequence complementary a codon that encodes Thr in the position of Ser in the conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region of a *Flaviviridae*;

Please replace the paragraph beginning on line 24, page 84, with the following amended paragraph:

In another embodiment, the invention provides a method for assaying a sample suspected of containing a Thr instead of a Ser in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region at the highly conserved at amino acid position 282 or a cytidine at nucleotide 8433 of the HCV genome, which indicates that the virus is hypersensitive to interferon treatment, comprising:

Please replace the paragraphs beginning on line 3, page 88, with the following amended paragraphs:

Other aspects of the present invention provide a method to treat a *Flaviviridae* infection by administering a therapeutically effective amount of a 2'-branched nucleoside, for example, a 2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC, or its pharmaceutically acceptable prodrug and/or salt, to a human in need of therapy, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a threonine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that is associated with such mutation. The codons ACA, ACG or ACU, which also encode Threonine, can be substituted for the codon ACC (in bold) in **Table 2** above to detect the presence of a Threonine in domain B of the RNA polymerase region of BVDV.

Another aspect of the present invention provides a method to treat and/or to substantially cure a *Flaviviridae* infection in a host infected with a *Flaviviridae* that contains a Serine to Threonine mutation in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region by administering a therapeutically effective amount of interferon. Therefore, in other embodiments of the present invention, the codons ACA, ACG or ACU, which also encode Threonine, can be substituted for the codon ACC (in bold) in **Table 2** above, for example to detect the presence of a Threonine at residue 405 of the RNA polymerase region of BVDV.

Please replace the paragraphs beginning on line 3, page 90, with the following amended paragraph:

Other aspects of the present invention provide a method to treat a *Flaviviridae* infection by administering a therapeutically effective amount of a 2'-branched nucleoside, for example, a 2'-branched pyrimidine nucleoside, for example β-D-2'-CH_3-riboC, or its pharmaceutically acceptable prodrug and/or salt, to a human in need of therapy, in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in a *Flaviviridae* at a location other than a mutation of a nucleotide that results in a change from serine to a threonine in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that is associated with such mutation. As before, the codons ACA, ACG or ACU, which also encode Threonine, can be substituted for the codon ACC (in bold) in **Table 3**, for example to detect the presence of a Threonine in domain B of the RNA polymerase region of HCV.

Another aspect of the present invention provides a method to treat and/or to substantially cure a *Flaviviridae* infection in a host infected with a *Flaviviridae* that contains a Serine to Threonine mutation in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region by administering a therapeutically effective amount of interferon. The codons ACA, ACG or ACU, which also encode Threonine, can be substituted for the codon ACC (in bold) in **Table 3**, as above, for example to detect the presence of a Threonine at residue 282 of the RNA polymerase region of HCV.

Please replace the paragraph beginning on line 17, page 114, with the following amended paragraph:

The present invention provides methods to achieve optimal treatment of a *Flaviviridae* infection through administration of a 2'-branched nucleoside, or a pharmaceutically acceptable prodrug and/or salt thereof, to a human in need of therapy in combination and/or alternation with one or more drugs that directly or indirectly induce a mutation in the viral genome at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, and/or one or more drugs that is associated with such mutation.

Please replace the paragraph beginning on line 21, page 116, with the following amended paragraph:

Any host, including a human, exhibiting an infection caused by a *Flaviviridae* virus can be treated by administering to the patient an effective amount of a 2'-branched nucleoside or a pharmaceutically acceptable prodrug and/or salt thereof, such as β-D-2'-CH_3-riboC or its 3'valine ester prodrug, in the presence of a pharmaceutically acceptable carrier or dilutant, for any of the indications or modes of administration as described in detail herein in combination or alternation with a drug that induces a mutation in the viral genome at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. The 2'-branched nucleoside, such as β-D-2'-CH_3-riboC, or a pharmaceutically acceptable prodrug and/or salt thereof can be administered alone or in combination or alternation with other antiviral agents as described herein. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

Please replace the paragraph beginning on line 14, page 121, with the following amended paragraph:

A number of patents disclose drug delivery systems that can be used to administer a 2'-branched nucleoside, or pharmaceutically acceptable prodrug and/or salt thereof, in combination and/or alternation with a drug that induces a mutation in the viral genome at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region. U.S. Patent No. 5,749,847 discloses a method for the delivery of nucleotides into organisms by electrophoration. U.S. Patent No. 5,718,921 discloses the use of microspheres comprising a polymer and drug dispersed therein as a delivery system. U.S. Patent No. 5,629,009 discloses a delivery system for the controlled release of bioactive factors. U.S. Patent No, 5,578,325 discloses the use of nanoparticles and microparticles of non-linear hydrophilic hydrophobic multiblock copolymers for drug delivery. U.S. Patent No. 5,545,409 discloses a delivery system for the controlled release of bioactive factors. U.S. Patent No. 5,494,682 discloses the use of ionically cross-linked polymeric microcapsules as a drug delivery system.

Please replace the Abstract, with the following amended Abstract:

The present invention discloses a method for the treatment of *Flaviviridae* infection that includes the administration of a 2'-branched nucleoside, or a pharmaceutically acceptable prodrug and/or salt thereof, to a human in need of therapy in combination or alternation with a drug that directly or indirectly induces a mutation in the viral genome at a location other than a mutation of a nucleotide that results in a change from serine to a different amino acid in the highly conserved consensus sequence, XRXSGXXXT (Sequence ID No. 63), of domain B of the RNA polymerase region, or is associated with such a mutation. The invention also includes a method to detect a mutant strain of *Flaviviridae* and a method for its treatment.

Please enter the attached Sequence Listing into the Specification.

Attachments: Nucleotide Sequence Listing in written form (13 pp.)
Diskette containing the Sequence Listing in computer readable form